REMARKS

In view of the above amendments and the following remarks, reconsideration of the outstanding office action is respectfully requested. Pursuant to 37 CFR § 1.21, attached as an Appendix is a Version With Markings to Show Changes Made.

The rejection of claims 1-8, 10, and 25 under 35 U.S.C. § 103 for obviousness over U.S. Patent No. 5,824,782 to Holzer et. al., ("Holzer") in view of Huston, et. al., "Protein Engineering of Single-Chain Fv Analogs and Fusion Proteins," Methods Enzymology 203: 46-88 (1991)("Huston") is respectfully traversed.

Holzer discloses immunoconjugates which comprise a monoclonal antibody or fragment thereof, which is specific for the human EGF-receptor molecule, and a member of the chemokine family. The member of the chemokine family is preferably selected from C-X-C family, such IL-8. The immunoconjugates induce cytotoxic and chemotactic activity and are suitable for a targeted tumor therapy. Holzer's immunoconjugate binds the N-terminus of IL-8 to the carboxy terminus of the Fab fragment of the monoclonal antibody. Thus, Holzer does not satisfy the requirement of the claimed invention that the chemokine be "coupled to the N-terminus of the heavy or light chain of the antibody".

The portion of Huston relied on in the outstanding office action relates to the protein engineering of single-chain Fv analogs and fusion proteins. In these constructs, the single-chain Fv analogs are variable region fragments of antibodies which consist of a heavy-chain variable region domain V_H non-convalently associated with a light-chain variable domain V_L in the form of a single chain. As explained on page 47, this single-chain Fv analog is prepared by connecting the genes encoding the V_H domain and the V_L domain with an oligonucleotide and recombinantly producing the V_H and V_L domains with a linker peptide between them. Thus, as noted in following passage on page 51, the single-chain Fv analog of Huston is distinguishable from the claimed complete antibody:

> The single-chain Fv consists of a single polypeptide chain with the sequence V_H-linker-V_L or V_L-linker-V_H, as opposed to the classical Fv heterodimer of V_H and V_L.

Moreover, native IgG antibodies not only contain V_H and V_L domains but also constant regions C_H1, C_H2, and C_H3, with all of these components arranged with respect to one another in the particular fashion shown in Figure 1A on page 49 of Huston. The single-chain Fv analogs of Huston not only lack the constant regions of IgG but also the native conformation of such antibodies. Since Huston does not utilize complete antibodies, it is clearly distinguishable from the claimed invention.

As demonstrated in the accompanying Declaration of Seung-Uon Shin under 37 C.F.R. § 1.132 ("Shin Declaration"), one of ordinary skill in the art would have no basis to adapt the teachings of Huston regarding single-chain Fv analogs to the whole antibody immunoconjugates of Holzer. In particular, scientists skilled in the field of antibody-based cancer therapeutics would not regard information relating to immunoconjugates of single chain Fv analogs as relevant to immunoconjugates made from whole antibodies (Shin Declaration ¶ 4). As explained below, there are significant differences with regard to the avidity, half life, and chemokine carriage which would cause scientists skilled in the field of antibody cancer therapeutics to avoid adapting single chain Fv analog technology to whole antibody cancer therapeutics (Id.).

With regard to avidity, whole antibodies have two binding sites, while single chain Fv analogs have one binding site (Shin Declaration ¶ 5). Although they have exactly the same affinities, whole antibodies show higher binding ability to antigen than single chain Fv analogs, because of the avidity of the former (Id.). This characteristic of whole antibodies will provide stronger binding to antigen than single chain Fv analogs (Id.). As a result, diffusion of whole antibody therapeutics into tumors is prevented and, by remaining on the surface of solid tumors, such therapeutics will have the tendency to achieve better recruitment of immune effector cells from the blood (Id.). Since it is very hard to obtain any antibody with an affinity of $>1 \times 10^{-10}$ M, the diminished affinity of single chain Fv analogs will tend to impair their ability to bind to tumors avidly *in vivo* (Id.). The difference in avidity between whole antibodies and single chain Fv analogs is demonstrated by Adams et al., "High Affinity Restricts the Localization and Tumor Penetration of Single-Chain FV Antibody Molecules," Cancer Res, 61(12):4750-5 (2001) (Shin Declaration ¶ 6).

The half-life of whole antibodies is generally much longer than that of single chain Fv analogs (Shin Declaration ¶ 7). This prolonged half-life of antibodies increases bioavailability to tumors (Id.). Since single chain Fv analogs possess a short half-life, they

must be frequently administered at a high dosage to achieve a desired anti-tumor efficacy (Id.). The difference in half-life between whole antibodies and single chain Fv analogs is demonstrated by Covell et al., "Pharmacokinetics of Monoclonal Immunoglobulin G1, F(ab')2, and Fab' in Mice," Cancer Res, 46(8):3969-78 (1986) and Goel et al., "^{99}mTc-Labeled Divalent and Tetravalent CC49 Single-Chain Fv's: Novel Imaging Agents for Rapid In Vivo Localization of Human Colon Carcinoma," J Nucl Med, 42(10):1519-27 (2001) (Shin Declaration ¶¶ 8-10).

Whole antibodies can carry two molecules of chemokines, but single chain Fv analogs carry only a single chemokine (Shin Declaration ¶ 11). Since chemokine receptors can form dimers, whole antibody fusion proteins carrying two chemokines would be much more effective cancer therapeutics than single chain Fv analog fusions (Id.). In addition, two chemokine molecules provide stronger binding to their receptors than single chain Fv analogs, which would be dimerized after chemokine binding to transmit intracellular signals (Id.).

G-protein coupled receptors constitute a large family of homologous transmembrane proteins which are activated by a variety of different ligands such as chemokine, neurokinin, opioid, somatostatin, thyrotrophinm, and the whole biogenic amine family (Shin Declaration ¶ 11). G-protein coupled receptor can dimerize with the dimer being the functionally active form of the receptor (Id.).

Thus, an antibody carrying two chemokine molecules would tend to be more efficient at signaling through facilitation of receptor dimerization and/or crosslinking (Shin Declaration ¶ 12). This is demonstrated by Gouldson et al., "Lipid-Facing Correlated Mutations and Dimerization in G-Protein Coupled Receptors," Protein Eng, 14(10):759-767 (2001) and Vila-Coro et al., "The Chemokine SDF-1alpha Triggers CXCR4 Receptor Dimerization and Activates the JAK/STAT Pathway," FASEB J, 13(13):1699-710 (1999) (Shin Declaration ¶¶ 13-15).

For all of these reasons, it is apparent that one of ordinary skill in the art of antibody cancer therapeutics would not adapt teachings relating to single chain Fv analogs to cancer therapeutics relying on whole antibodies. Accordingly, the rejection based on the combination of Holzer and Huston should be withdrawn.

The rejection of claims 1, 3-10, and 25 under 35 U.S.C. § 112 (2nd para.) for indefiniteness is respectfully traversed in view of the above amendments.

The rejection of claims 1 and 9 under 35 U.S.C. § 103 for obviousness over Huston in view of U.S. Patent No. 5,514,554 to Bacus ("Bacus") and Holzer is respectfully traversed. Bacus is cited as teaching monoclonal antibodies to her2/neu and does not overcome the above-noted deficiencies of Holzer and Huston. Accordingly, the rejection based on the combination of Huston, Bacus, and Huston should be withdrawn.

In view of all the foregoing, it is submitted that this case is in condition for allowance and such allowance is earnestly solicited.

Respectfully submitted,

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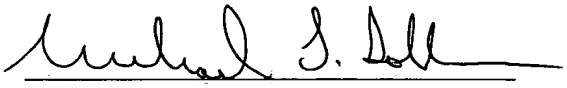

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